

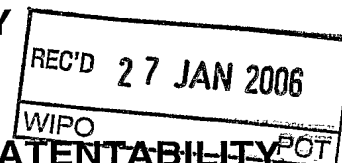
## PATENT COOPERATION TREATY


PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference PC26158A		<b>FOR FURTHER ACTION</b>	See Form PCT/IPEA/416
International application No. PCT/IB2004/003668	International filing date (day/month/year) 08.11.2004	Priority date (day/month/year) 20.11.2003	
International Patent Classification (IPC) or national classification and IPC C07D213/74, A61K31/4965			
Applicant WARNER-LAMBERT COMPANY LLC			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 4 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input checked="" type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand  17.12.2004		Date of completion of this report  25.01.2006	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer  Zellner, A  Telephone No. +49 89 2399-8078	



**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/IB2004/003668

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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements**\* of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-35 as originally filed

**Claims, Numbers**

1-14 filed with telefax on 14.04.2005

**Drawings, Sheets**

1/1 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/B2004/003668

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-14
	No: Claims	
Inventive step (IS)	Yes: Claims	1-14
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-14
	No: Claims	

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

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**Box No. VII Certain defects in the international application**

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The following defects in the form or contents of the international application have been noted:

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

1. The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: DE 22 30 392 A1 (CASSELLA FARBWERKE MAINKUR A.-G.) 31 January 1974  
D2: EP-A1-0 293 744 (BASF A.-G., FED. REP. GER.) 7 December 1988  
D3: WO 03/002544 A (BRISTOL-MYERS SQUIBB COMPANY; PHARMACOEPIA, INC; AHMED, GULZAR; METZGE) 9 January 2003  
D4: US 2003/186984 A1 (ACKERMANN, JEAN ET AL) 2 October 2003  
D5: WO 2004/058174 A (BAYER PHARMACEUTICALS CORPORATION; CANTIN, LOUIS-DAVID; CHOI, SOONGYU;) 15 July 2004  
D6: EP-A-1 122 242 (YAMANOUCHI PHARMACEUTICAL CO. LTD) 8 August 2001

2. The present application relates to pyridine derivatives and their use as androgen modulators.
3. The amendments filed with letter dated 14.04.2005 are in accordance with the requirements of Art. 34(2)(b) PCT.

item V

4. Novelty (Art. 33(2) PCT)

The compounds disclosed in Documents D1-D4 are not considered falling within the scope of amended claim 1 due to the restriction of substituent R<sup>1</sup>. The requirements of Art. 33(2) PCT are thus fulfilled.

5. Inventive step (Art. 33(3) PCT)

Document D6 relates to compounds with anti-androgen action (see the abstract). The presently claimed compounds differ from compound 1-23 (table 7, p. 32 of D6) in an additional substituent R<sup>1</sup> and in that the N-atom does not form part of a cyclic structure. It would appear that the provision of compounds according to present claim 1 cannot be considered obvious for the skilled person when starting from the disclosure of D6 in order to solve the technical problem of providing further compounds useful as androgen

modulators. The claimed subject-matter which can thus be considered based on an inventive step as well. The application meets the requirements of Art. 33(3) PCT.

6. Industrial applicability (Art. 33(4) PCT)

Can be acknowledged for claims 1-14.

item **VI**

7. Document D5 was published after the priority date of the present application but before its international filing date. Its content would be considered as forming part of the state of the art if the priority of the present application was found to be invalid. When entering the regional european phase the document will also be considered for the question of novelty even if the presently claimed priority is valid. Examples 310-312 of D5 do not fall within the scope of amended claim 1 due to the amendment of the definition for R<sup>1</sup>.

item **VII**

8. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the cited documents is not mentioned in the description, nor are these documents identified therein.

item **VIII**

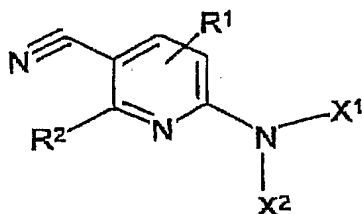
9. The expression "prodrug" does not have a precise meaning in the art and is thus not considered suitable to define subject-matter. Claim1 is thus not considered clear within the meaning of Art. 6 PCT.
10. Claims 9 and 10 are not acceptable under Art. 6 PCT. The therapeutic application is either not defined at all (claim 9) or functionally defined by a mechanism of action (claim 10) which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).

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## CLAIMS

What is claimed is:

1. A compound of the formula:



and the pharmaceutically acceptable salts, hydrates, and prodrugs thereof, wherein;

- a)  $R^1$  is represented by  $(C_1-C_2)$ alkyl, substituted with one or more halogens, or  $(C_1-C_2)$ alkoxy, substituted with one or more halogens,
- b)  $R^2$  is represented by hydrogen or halogen,
- c)  $X^1$  and  $X^2$  are each independently represented by
  - i)  $(C_1-C_{12})$ alkyl, optionally substituted,
  - ii)  $(C_2-C_{12})$ alkenyl, optionally substituted,
  - iii)  $(C_2-C_{12})$ alkynyl, optionally substituted,
  - iv)  $(C_3-C_{10})$ cycloalkyl, optionally substituted,
  - v)  $(C_3-C_{10})$ cycloalkyl $(C_1-C_6)$ alkyl, in which the alkyl and cycloalkyl moieties may each be optionally substituted,
  - vi)  $(C_6-C_{10})$ aryl, optionally substituted,
  - vii)  $(C_6-C_{10})$ aryl $(C_1-C_6)$ alkyl, in which both the alkyl and aryl moieties may be optionally substituted,
  - viii)  $-(CH_2)_q-CH_2-ZH$ , in which Z is S or O and q is an integer from 1-11,
  - ix)  $-(CH_2)_n-Y-(CH_2)_p-CH_3$ , in which Y is O or S, n is an integer from 1 to 4, and p is an integer from 1 to 4,
  - x)  $-[CH_2]_m-C(O)R^3$ , in which m is an integer selected from 1 to 8 and  $R^3$  is represented by hydrogen,  $(C_1-C_{12})$ alkyl,  $(C_6-C_{10})$ aryl, or  $(C_6-C_{10})$ aryl $(C_1-C_6)$ alkyl, in which both the alkyl and aryl moieties may be optionally substituted,
  - xi)  $-[CH_2]_m-C(O)-O-R^4$ , in which m is as defined above and  $R^4$  is represented by hydrogen,  $(C_1-C_{12})$ alkyl,  $(C_6-C_{10})$ aryl, or

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(C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, in which the alkyl and aryl moieties may be optionally substituted,

xii) -[CH<sub>2</sub>]<sub>m</sub>-C(O)-NR<sup>5</sup>R<sup>6</sup> in which m is as described above, and R<sup>5</sup> and R<sup>6</sup> are each independently represented by hydrogen, (C<sub>1</sub>-C<sub>12</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, or (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, in which the alkyl and aryl moieties may each be optionally substituted,

i) heteroaryl, optionally substituted,

ii) heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, in which the heteroaryl and alkyl moieties may each be optionally substituted,

iii) heterocyclic, optionally substituted, or,

iv) heterocyclic(C<sub>1</sub>-C<sub>6</sub>)alkyl, in which the alkyl and heterocyclic moieties may each be optionally substituted.

2. A compound according to claim 1 in which R<sup>1</sup> is represented by trifluoromethyl.

3. A compound according to any one of claims 1- or 2 in which said trifluoromethyl is located at the 4-position of the pyridine ring.

4. A compound according to anyone of claims 1-3 in which R<sup>2</sup> is hydrogen.

5. A compound according to anyone of claims 1-4 in which X<sup>1</sup> is (C<sub>1</sub>-C<sub>12</sub>)alkyl and X<sub>2</sub> is (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl.

6. A compound according to anyone of claims 1-5 in which X<sup>1</sup> and X<sup>2</sup> are each (C<sub>1</sub>-C<sub>12</sub>)alkyl

7. A compound according to anyone of claims 1-6 in which X<sup>1</sup> is (C<sub>1</sub>-C<sub>12</sub>)alkyl and X<sub>2</sub> is (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl.

8. A compound according to claim 1 selected from the group consisting of (R)-(+)-6-[Methyl-(1-Phenyl-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile,

(R)-(+)-2-Chloro-6-[methyl-(1-phenyl-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile,

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- 5 6-[methyl-(1-phenyl-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile,  
 6-[methyl-(1-phenyl-ethyl)-amino]-4-trifluoromethoxy-nicotinonitrile,  
 6-[methyl-(1-(4-fluorophenyl)-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile,  
 6-[methyl-(1-(3-hydroxyphenyl)-ethyl)-amino]-4-trifluoromethyl-  
 10 nicotinonitrile,  
 6-[butyl(1-(3-hydroxyphenyl)-ethyl)-amino]-4-trifluoromethoxy-  
 nicotinonitrile,  
 6-dipropylamino-4-trifluoromethyl-nicotinonitrile,  
 2-chloro-6-dimethylamino-4-trifluoromethyl-nicotinonitrile,  
 10 6-(hexyl-octyl-amino)-4-trifluoromethyl-nicotinonitrile,  
 6-(sec-butyl-methyl-amino)-4-trifluoromethyl-nicotinonitrile,  
 6-[butyl-(2-hydroxy-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile,  
 6-(butyl-methyl-amino)-4-trifluoromethyl-nicotinonitrile,  
 6-(benzyl-methyl-amino)-4-trifluoromethyl-nicotinonitrile,  
 15 6-(cyclohexyl-propyl-amino)-4-trifluoromethyl-nicotinonitrile,  
 6-(cyclopropylmethyl-propyl-amino)-4-trifluoromethyl-nicotinonitrile,  
 6-(sec-butyl-methyl-amino)-2-chloro-4-trifluoromethyl-nicotinonitrile,  
 6-Dipropylamino-2-chloro-4-trifluoromethyl-nicotinonitrile,  
 6-(propyl-methyl-amino)-2-chloro-4-trifluoromethyl-nicotinonitrile, and,  
 20 6-(Butyl-methyl-amino)-2-chloro-4-trifluoromethyl-nicotinonitrile.

9. Use of a compound according to anyone of Claims 1-8 in the manufacture  
 of medicament.
10. Use of a compound according to anyone of Claims 1-8 in the  
 25 manufacture of a medicament for inhibiting activation of the androgen  
 receptor.
11. A pharmaceutical composition comprising a compound according to any  
 one of Claims 1-8 in admixture with 1, or more, pharmaceutically  
 acceptable excipients.
12. A topical pharmaceutical formulation comprising a compound according to  
 30 anyone of Claims 1-8 in admixture with 1, or more, pharmaceutically  
 acceptable excipients suitable for dermal application.



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13. An article of manufacture comprising a compound according to any one of Claims 1-8 packaged for retail distribution which advises a consumer how to utilize the compound to alleviate a condition selected from the group consisting of acne, alopecia, and oily skin.

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14. Use of a compound according to any one of claims 1-8 in the manufacture of a medicament for alleviating a condition selected from the group consisting of hormone dependent cancers, benign hyperplasia of the prostate, acne, hirsutism, excess sebum, alopecia, premenstrual syndrome, lung cancer, precocious puberty, osteoporosis, hypogonadism, age-related decrease in muscle mass, and anemia.

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